PATENT SPECIFICATION (11) 1355866

1355866

(21) Application No. 36235/71 (22) Filed 2 Aug. 1971
(31) Convention Application No. 11922 (32) Filed 6 Aug. 1970
(31) Convention Application No. 7915 (32) Filed 1 June 1971 in
(33) Switzerland (CH)
(44) Complete Specification published 5 June 1974
(51) International Classification C07D 99/02; A61K 27/00
(52) Index at acceptance
C2C 1626 1739 213 215 220 226 227 22Y 246 247 250 252 255 25Y 28X 29X 29Y 305 30Y 311 313 31Y 321 32Y 332 337 339 349 351 352 360 361 364 366 368 36Y 373 37X 37Y 396 43X 440 443 464 491 551 552 553 613 614 620 623 625 628 652 658 65X 660 661 695 699 762 790 79Y BG QL QS RN RU

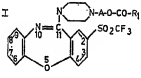
(72) Inventors JEAN SCHMUTZ, FRITZ HUNZIKER and FRANZ MARTIN KÜNZLE

(54) DIBENZOXAZEPINE DERIVATIVES

(71) We, WANDER LTD., formerly Dr. A. Wander Ltd. of 115 Monbijoustrasse, 3001 Berne, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to dibenz[b,f][1,4]-oxazepine derivatives.

More particularly, this invention provides compounds of formula I,



I

wherein A signifies a straight or branched chain alkylene group of 1 to 3 carbon atoms, and

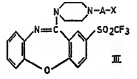
R_1 signifies a straight or branched chain, saturated or unsaturated, aliphatic hydrocarbon radical of 3 to 18 carbon atoms.

The invention also provides processes for the production of the compounds of formula I, characterized by

a) reacting a compound of formula VIII,

$$R_1—COOH \qquad \text{VIII}$$

wherein R_1 is as defined above, or a salt thereof, an acid halide thereof or an acid anhydride thereof with a compound of formula III,

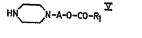


III

wherein A is as defined above, and

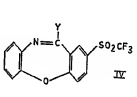
X signifies a hydroxyl group, a group of formula —OMe, wherein Me signifies a metal, halogen or tosyl, or

b) reacting a compound of formula V,



V

wherein A and R_1 are defined above, with a compound of formula IV,

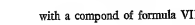


IV

wherein Y is halogen, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms, sulph hydryl, p-nitrobenzylthio, or tosyl, or

c) reacting the compound of formula VI

with a compound of formula VII,



wherein A and R_1 are as defined above, and Z is a halogen or tosyl.

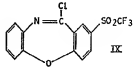
Process a) is conveniently carried out in an inert organic solvent, eg. benzene, toluene or pyridine, and at a temperature of from about room temperature to about 50° C. The reaction time may, for example, vary from 1 to 24 hours. A preferred acid halide is the acid chloride. Suitable salts of the compound of formula VIII include the silver salt. Where X in the compound of formula III signifies the group —OMe, Me preferably signifies an alkali metal. Where X signifies halogen, this is preferably a chlorine atom. As will be appreciated by those skilled in the art, where X, in the compound of formula III, signifies a hydroxy group, the free acid of formula VIII or an acid halide or acid anhydride thereof may be employed; where X signifies the group —OMe, an acid halide or acid anhydride of a compound of formula VIII may be employed, and where X signifies halogen or trosyl, a salt of the compound of formula VIII may be employed. When a compound of formula III is employed in free acid form, and, particularly, when an acid halide or anhydride of a compound of formula VIII is employed, the process may suitably be carried out in the presence of an acid-binding agent, e.g. triethylamine.

Process b) is suitably effected in an inert organic solvent, e.g. xylene, and at a temperature of from 50° C to the reflux temperature of the reaction medium, preferably at the reflux temperature of the reaction medium. The reaction time may, for example, be about 5 hours. When Y is alkoxy or arkylthio, this suitably is methoxy or methylthio respectively.

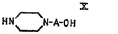
Process c) is conveniently effected at a temperature of from 50° C to the reflux temperature of the reaction mixture, and in the presence of an inert organic solvent, e.g. dioxane, toluene or an alcohol, e.g. ethanol. The process is suitably carried out in the presence of an acid-binding agent, e.g. potassium carbonate. In the compound of formula VII, when Z is a halogen atom, this is, preferably a chlorine atom.

The resulting compounds of formula I may be isolated and purified using conventional techniques. Where required, free base forms of the compounds may be converted into acid addition salt forms in conventional manner, and *vice versa*.

The compounds of formula III, wherein X signifies a hydroxyl group, used as starting materials in process a), may, for example, be obtained by reacting the imide chloride of formula IX



with a piperazine derivative of formula X,

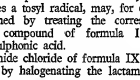


wherein A is as defined above.

The process may be carried out in conventional manner.

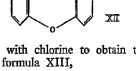
The remaining compounds of formula III may be produced in conventional manner from the compounds of formula III, wherein X signifies a hydroxyl group. Thus, for example, the compounds of formula III, wherein X signifies a halogen atom, may, for example, be obtained by halogenating the corresponding hydroxy compound of formula III. Furthermore, the compounds of formula III, wherein X signifies a tosyl radical, may, for example, be obtained by treating the corresponding hydroxy compound of formula III with toluene-sulphonic acid.

The imide chloride of formula IX may be obtained by halogenating the lactam of formula XI

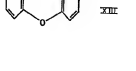


in conventional manner, for example employing phosphorous oxychloride. The lactam XI may, for example, be produced as follows:

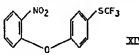
2-Nitro-4'-methylthio-diphenyl oxide of formula XII



is reacted with chlorine to obtain the compound of formula XIII,

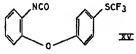


and this is treated with antimony trifluoride. The resulting compound of formula XIV



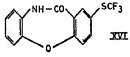
XIV

is reduced to the amine and this is converted with phosgene into the isocyanate of formula XV.



XV

Ring closure of the isocyanate of formula XV with phosphorus oxychloride and phosphorous pentoxide yields the lactam of formula XVI,



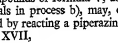
XVI

and this is oxidized with hydrogen peroxide to obtain the lactam of formul XI.

The above described reactions for producing the compound of formula XI may all be effected in conventional manner, for example as illustrated in the Examples hereinafter.

The compounds of formula IV, used as starting materials in process b), may be produced in conventional manner. Thus, for example, that in which X signifies a sulphhydryl group may be produced conventionally from the lactam of formula XI, and those in which Y signifies an alkylthio or *p*-nitrobenzylthio group may be produced from the sulphhydryl compound by alkylation or aralkylation. Those in which Y signifies a halogen atom, e.g. a chlorine atom, may be obtained in conventional manner by treating the lactam of formula XI with a halogenating agent, e.g. phosphorus oxychloride or pentachloride, suitably in the presence of a catalytic amount of dimethyl aniline or dimethyl formamide.

The compounds of formula V, used as starting materials in process b), may, for example, be obtained by reacting a piperazine derivative of formula XVII,

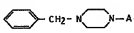


XVII

wherein A is as defined above, and Hal signifies a halogen atom, with a silver salt of a compound of formula VIII, in conventional manner.

The halogen compound of formula XVII may, for example, be obtained by halogenating the corresponding alcohols, which are either known or may be produced in conventional manner.

The compounds of formula V may also be obtained by reacting a compound of formula XVIII,



XVIII

wherein A is as defined above, with a compound of formula VIII, stated above, or a reactive derivative thereof, and, subsequently, hydrogenolytically removing the benzyl group from the reaction product.

The compounds of formula XVIII are known or may be produced in conventional manner.

The 2-trifluoromethylsulphonyl-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine, used as starting material in process c), may, for example, be obtained by reacting a compound of formula IV with piperazine, in conventional manner.

The compounds of formula VII, used as starting materials in process c), may, for example, be obtained by reacting a compound of formula XIX,

Z—A—OH XIX

wherein A and Z are as defined above, with a compound of formula VIII, stated above, or a reactive acid derivative thereof.

The compounds of formula XIX are known or may be produced in conventional manner.

The compounds of formula I possess pharmacological activity. In particular, they possess central nervous system activy, neuroleptic and antiemetic activity, as indicated, e.g., by an apomorphine-antagonistic effect in rats [method of Janssen et al., Arzneimittelforschung *10*, 1003 (1960)]. The compounds furthermore exhibit a depot effect. The compounds are therefore indicated for use as neuroleptic and antiemetic agents.

An indicated suitable dosage is from 20 to 100 mg administered in a single dose every one to three weeks, and administered parenterally, particularly intramuscularly.

The invention provides a pharmaceutical composition comprising a compound of formula I in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Preferably the pharmaceutical composition is in a form suitable for parenteral administration, e.g. as injectable solutions or suspensions. For parenteral administration, suitable preparations may comprise a solution of a compound of formula I in an oil, for example a 1 to 3% solution in a vegetable oil, such as sesame oil, peanut oil and olive oil, or, preferably, in a glyceride of a saturated

fatty acid having a mean chain length (C_7—C_{11}) of the Migylol type (Miglyol is a registered Trade Mark). The oily solutions, which are indicated for intramuscular administration, may be sterilized by germ filtration and subsequent heating to 120° C for 20 minutes.

The compounds of formula I may be used in free base form or in the form of pharmaceutically acceptable acid addition salts, which salt forms have the same order of activity as the free base forms. Suitable acids for salt formation include organic acids, such as toluenesulphonic, malonic, succinic, malic, maleic and tartaric acid, and inorganic acids, such as a hydrohalic acid, sulphuric, nitric and phosphoric acid.

The preferred compounds of formula I are 2 - trifluoromethysulphonyl - 11 - (4 - 8-tetradecanoyloxyethyl - 1 - piperazinyl)dibenz-[b,f] [1,4]-oxazepine and 2-trifluoromethylsulphonyl - 11 - (4 - 8 - decanoyloxyethyl - 1-piperazinyl)dibenz[b,f] [1,4] oxazepine.

The following Examples illustrate the invention.

EXAMPLE 1:

2 - Trifluoromethylsulphonyl - 11 - (4 - β-heptanoyloxyethyl - 1 - piperazinyl)dibenz-[b,f] [1,4]oxazepine [process a)]

1 g of 2-trifluoromethylsulphonyl-11-(4-β-hydroxyethyl - 1 - piperazinyl)dibenz[b,f]-[1,4] oxazepine is dissolved in 20 cc of absolute pyridine, 1.1 g of enanthic acid chloride are added to the solution and this is allowed to stand over night. The reaction mixture is strongly concentrated by evaporation in a vacuum and water is added to the residue. The reaction mixture is rendered alkaline with caustic soda solution and is subsequently extracted with ether. The ether phase is repeatedly washed with water, dried over sodium sulphate, clarified with active charcoal and concentrated by evaporation. 2-Trifluoromethylsulphonyl - 11 - (4 - β - heptanoyloxyethyl - 1 - piperazinyl)dibenz[b,f] [1,4] oxazepine is obtained as residue in the form of a yellowish oil which cannot be crystallized. Thin layer chromatogram: see Table.

The 2 - trifluoromethylsulphonyl - 11 - (4-β - hydroxyethyl - 1 - piperazinyl)dibenz[b,f]-[1,4]oxazepine, used as starting material in this process, may be obtained as described below:

52.2 g of 2-nitro-4'-methylthio-diphenyl oxide (M.P. 59—61° C) are dissolved in 1.5 liters of chloroform and chlorination is effected at 20° C while exposing to light and passing a total of 43 g of chlorine gas into the solution. The residue obtained after concentrating the reaction mixture by evaporation in a vacuum is crystallized from ether/petroleum ether, whereby 2-nitro-4'-trichloromethylthiodiphenyl oxide, having a M.P. of 76—79° C, is obtained.

61.3 g of this product are dissolved in 280 cc of Sulfolane and heated to 150° C within 30 minutes with 41 g of antimony trifluoride. The reaction mixture is kept at this temperature for 1½ hours, a large amount of dilute hydrochloric acid is added and extraction is effected with ether. The organic phase is washed with dilute hydrochloric acid and dilute caustic soda solution, is dried over sodium sulphate and evaporated to dryness in a vacuum. 2-Nitro-4'-trifluoromethylthio-diphenyl oxide, having a B.P. of 125—130° C/0.1 mm of Hg, is obtained as residue and may be crystallized from ether/petroleum ether to obtain yellowish crystals having a M.P. of 40—42° C.

27.8 g of this compound are hydrogenated in glacial acetic acid with Raney nickel at normal pressure and 20° C. 2-Amino-4'-trifluoromethylthio-diphenyl oxide is obtained as colourless oil having a B.P. of 110—114° C/0.05 mm of Hg.

26 g of 2-amino-4'-trifluoromethylthio-diphenyl oxide are added dropwise while stirring to 150 cc of an approximately 20% solution of phosgene in absolute toluene. The reaction mixture is subsequently heated to the boil under reflux for 15 minutes while passing phosgene into the solution. After removing the toluene by distillation, the residue is fractionated in a vacuum. 2-Isocyanato-4'-trifluoromethylthio-diphenyl oxide is obtained as colourless oil having a B.P. of 110—115° C/0.07 mm of Hg.

3 g of this product are heated to the boil under reflux for 24 hours with 40 cc of phosphorus oxychloride and 4 g of phosphorus pentoxide. The reaction mixture is concentrated by evaporation in a vacuum, ice is added to the resulting viscous residue while cooling, the mixture is rendered almost neutral with concentrated caustic soda solution, is allowed to stand for 24 hours and is extracted with ether. The ether phase is washed with water and aqueous sodium chloride solution, is dried over sodium sulphate and strongly concentrated by evaporation. After the addition of petroleum ether, 2-trifluoromethylthio-10,11-dihydro-11-oxodibenz[b,f] [1,4]oxazepine is obtained in the form of crystals having a M.P. of 215—216° C.

2.5 g of this compound are suspended in 50 cc of glacial acetic acid and 4 cc of a 30% hydrogen peroxide solution are added. The reaction mixture is heated to 70° C for 1 hour and subsequently to 100—110° C for 1½ hours. Water is added to the reaction mixture, this is concentrated in a vacuum and the resulting mash is filtered with suction and taken up in ether. The ether phase is washed with water, dilute caustic soda solution and aqueous sodium chloride solution, is dried over sodium sulphate, treated with active charcoal and filtered through a small amount of aluminium oxide. The filtrate is concentrated and petroleum ether is added. The pre-

cipitated crystals are separated and recrystallized from acetone/petroleum ether. 2-Trifluoromethylsulphonyl - 10,11 - dihydro - 11-oxo-dibenz[b,f] [1,4]oxazepine, having a M.P. of 193—198° C, is obtained.

4.5 g of this product are heated to the boil under reflux for 4½ hours with 100 cc of phosphorus oxychloride and 2 cc of N,N-dimethyl aniline. After removing the excess phosphorus oxychloride by distillation in a vacuum, the residue is dissolved in 120 cc of xylene and poured in ice/water. The xylene phase is washed with dilute hydrochloric acid and with water, is dried over sodium sulphate and concentrated to 100 cc in a vacuum. The solution, containing 2-trifluoromethylsulphonyl - 11 - chloro - dibenz[b,f] [1,4]-oxazepine, is heated to the boil under reflux for 5 hours with 12 g of N-(β-hydroxyethyl-piperazine. The reaction mixture is washed with dilute caustic soda solution and with water and is then exhaustively extracted with dilute hydrochloric acid. The acid extracts are rendered alkaline with concentrated caustic soda solution and the precipitated base is extracted with ether. The ether phase is washed with water, dried over sodium sulphate, filtered and concentrated by evaporation. The residue is crystallized from ether/petroleum ether, whereby 2-trifuoromethylsulphonyl-11-(4 - β - hydroxyethyl - 1 - piperazinyl)dibenz-[b,f] [1,4]oxazepine is obtained in the form of prisms having a M.P. of 121—123° C.

EXAMPLE 2:

2 - Trifluoromethylsulphonyl - 11 - (4 - β-tetradecanoyloxyethyl - 1 - piperazinyl)-dibenz[b,f] [1,4]oxazepine [process a)]

2 - Trifluoromethylsulphonyl - 11 - (4 - β-tetradecanoyloxyethyl - 1 - piperazinyl)dibenz-[b,f] [1,4]oxazepine is obtained in the form of a yellowish oil, which cannot be crystallized, by the process described in Example 1, except that 0.5 g of 2-trifluoromethylsulphonyl-11 - (4 - β - hydroxyethyl - 1 - piperazinyl)-dibenz[b,f] [1,4]oxazepine, 10 cc of absolute pyridine and 0.5 cc of myristic acid chloride are used as starting materials.

Thin layer chromatogram: see Table.

EXAMPLE 3:

2 - Trifluoromethylsulphonyl - 11 - (4 - β-butanoyloxyethyl - 1 - piperazinyl)dibenz-[b,f] [1,4]oxazepine [process a)]

2 - Trifluoromethylsulphonyl - 11 - (4 - β-butanoyloxyethyl - 1 - piperazinyl)dibenz[b,f]-[1,4]oxazepine is obtained in the form of a yellowish oil, which cannot be crystallized, by the process described in Example 1, except that 0.5 cc of butyric acid chloride is used as starting material.

Thin layer chromatogram: see Table.

EXAMPLE 4:

2 - Trifluoromethylsulphonyl - 11 - (4 - β-decanoyloxyethyl - 1 - perazinyl)dibenz-[b,f] [1,4]oxazepine [process a)]

2 - Trifluoromethylsulphonyl - 11 - (4 - β-decanoyloxyethyl - 1 - piperazinyl)dibenz-[b,f] [1,4]oxazepine is obtained in the form of a yellowish oil, which cannot be crystallized, by the process described in Example 1, except that 0.5 cc of capric acid chloride is used as starting material.

Thin layer chromatogram: see Table.

EXAMPLE 5:

2 - Trifluoromethylsulphonyl - 11 - (4 - β-heptaoyloxyethyl - 1 - piperazinyl)dibenz-[b,f] [1,4]oxazepine [process c)]

2.0 g of enanthic acid chloroethyl ester are added to a solution of 4.1 g of 2-trifluoromethylsulphonyl - 11 - (1 - piperazinyl)-dibenz [b,f] [1,4]oxazepine in 70 cc of toluene and the mixture is heated to 80° C for 4 hours. The mixture is subsequently concentrated by evaporation, water is added to the evaporation residue, this is rendered alkaline with concentrated caustic soda solution and extraction is effected with ether. The ethereal solution is washed with water and aqueous sodium chloride solution, is dried over sodium sulphate and concentrated by evaporation. The resulting yellow oil is dissolved in a mixture of ether/petroleum ether (1:4) and chromatographed on neutral aluminium oxide. After concentrating the eluates, 2-trifluoromethylsulphonyl - 11 - (4 - β - heptanoyloxyethyl-1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine is obtained in the form of a light yellow oil which is identical with the product obtained in accordance with Example 1.

The 2-trifluoromethylsulphonyl-11-(1-piperazinyl)dibenz[b,f] [1,4]oxazepine, employed as starting material, may be produced in the manner described in Example I for the production of 2-trifluoromethyl-11-(4-β-hydroxyethyl - 1 - piperazinyl)dibenz[b,f]-[1,4]oxazepine, expect that 20 cc of piperazine are employed in place of N-(β-hydroxyethyl)piperazine.

EXAMPLE 6:

2 - Trifluoromethylsulphonyl - 11 - (4 - β-heptanoyloxyethyl - 1 - piperazinyl)dibenz-[b,f] [1,4]oxazepine [process b)]

4.5 g of 2-trifluoromethylsulphonyl-10,11-dihydro-11-oxo-dibenz[b,f] [1,4]oxazepine are heated under reflux for 4½ hours with 75 cc of phosphorus oxychloride and 1.5 cc of N,N-dimethyl aniline. The excess phosphorus oxychloride is removed by distillation in a vacuum, ice is added to the residue and extraction is effected with xylene. The xylene solution is washed with 2 N hydrochloric acid,

water and aqueous sodium chloride solution, is dried over sodium sulphate, treated with active charcoal, filtered and somewhat concentrated. 3.6 g of 1-(β-heptanoyloxyethyl)-piperazine are added to this solution of 2-trifluoromethylsulphonyl - 11 - chloro - dibenz-[b,f] [1,4] oxazepine and heating to the boil under reflux is effected for 5 hours. The reaction mixture is subsequently evaporated to dryness and the residue is dissolved in water. The aqueous solution is rendered alkaline with concentrated caustic soda solution while adding some ice and extraction is effected with ether. The ethereal phase is washed with water and subsequently extracted with 2 N-hydrochloric acid. Ice is added to the hydrochloric acid solution and this is rendered alkaline with concentrated caustic soda solution. The separated oily product is extracted with ether, washed with water and aqueous sodium chloride solution and dried over sodium sulphate. After concentrating by evaporation, a light yellow oil is obtained, which is dissolved in a mixture of one part of ether and four parts of petroleum ether. The solution is filtered through neutral aluminium oxide and concentrated by evaporation. 2-Trifluoromethylsulphonyl - 11 - (4 - β - heptanoyloxyethyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine is obtained in the form of a light yellow oil which is identical with the products obtained in accordance with Examples 1 and 5.

The 2-triflouromethylsulphonyl-10,11-dihydro - 11 - oxo - dibenz[b,f] [1,4]oxazepine, used as starting material in this Example, may be obtained as described in Example 1.

The 1-(β-heptanoyloxyethyl)piperazine, likewise used as starting material in this Example, is obtained as follows:

17 g of enanthic acid chloride are added dropwise while stirring to 22 g of 4-benzyl piperazine-1-ethanol in 100 cc of chloroform. The mixture is subsequently heated in a steam bath for 15 minutes. The chloroform is removed in a vacuum, water is added to the residue, this is rendered alkaline with concentrated caustic soda solution and extracted thrice with ether. The ethereal extract is washed with water and aqueous sodium chloride solution, is dried over sodium sulphate, filtered through active charcoal and concentrated by evaporation. The residue is dissolved in petroleum ether and the solution is filtered through a small amount of aluminium oxide and concentrated by evaporation. 1-Benzyl-4-(β-heptanoyloxyethyl)-piperazine is obtained in the form of a colourless oil.

15 g of this product are dissolved in 50 cc of ethanol, the solution is rendered slightly acid with hydrochloric acid in ethanol and is concentrated. After the addition of ether, the dihydochloride crystallizes, is filtered with suction and dried. 17.5 g of the resulting dihydrochloride are dissolved in 300 cc of ethanol and 16.2 g of the corresponding free base are added. 1 g of 5% palladium charcoal are added to the solution and hydrogenolysis is effected at room temperature and normal pressure for 6 hours. After filtering off the catalyst, the filtrate is concentrated by evaporation in a vacuum, the residue is dissolved in ethanol and a solution of hydrochloric acid in ethanol is added. After the addition of ether, 1-(β-heptanoyloxyethyl)piperazine dihydrochloride, having a M.P. of 172—180° C, crystallizes. The base is liberated from the dihydrochloride by treatment with sodium ethanolate in ethanol.

EXAMPLE 7:

[processes b) and c)]

In manner analogous to Example 5 or 6, and employing appropriate starting materials in approximately equivalent amounts, the following compounds may be obtained:

2 - Trifluoromethylsulphonyl - 11 - (4 - β-tetradecanoyloxyethyl - 1 - piperazinyl)-dibenz[b,f] [1,4] oxazepine,

2 - trifluoromethylsulphonyl - 11 - (4 - β-butanoyloxyethyl - 1 - piperazinyl-dibenz[b,f] [1,4] oxazepine, and

2 - trifluoromethylsulphonyl - 11 - (4 - β-decanoyloxyethyl - 1 - piperazinyl)-dibenz[b,f] [1,4] oxazepine.

Having regard to section 9 of the Patents Act, reference is directed to the claim of our patent specification No. 1,318,401.

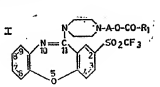
Table of thin layer chromatograms

(layer: silica gel SL 254 Antec)

Example	Eluting agent		Indicator	Rf value
1	a) chloroform/methanol/diethylamine	(8:1:1)	Dragendorff's reagent	0.84
	b) chloroform/methanol/glacial acetic acid	(8:1:1)	„ „	0.79
	c) ethyl acetate/glacial acetic acid/water	(5:2:2)	„ „	0.93
2	a) chloroform/cyclohexane/diethylamine	(5:4:1)	Dragendorff's reagent	0.76
	b) chloroform/methanol/glacial acetic acid	(8:1:1)	„ „	0.91
3	a) chloroform/cyclohexane/diethylamine	(5:4:1)	Dragendorff's reagent	0.63
	b) chloroform/methanol/glacial acetic acid	(8:1:1)	„ „	0.68
	c) ethyl acetate/glacial acetic acid/water	(5:2:2)	„ „	0.87
4	a) chloroform/cyclohexane/diethylamininc	(5:4:1)	Dragendorff's reagent	0.64
	b) chloroform/methanol/glacial acetic acid	(8:1:1)	„ „	0.82

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,



wherein A signifies a straight or branched chain alkylene group of 1 to 3 carbon atoms, and

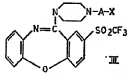
R_1 signifies a straight or branched chain, saturated or unsaturated, aliphatic hydrocarbon radical of 3 to 18 carbon atoms,

characterized by

a) reacting a compound of formula VIII,

R_1—COOH VIII

wherein R_1 is as defined above, or a salt thereof, an acid halide thereof or an acid anhydride thereof with a compound of formula III,

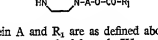


III

wherein A is as defined above, and

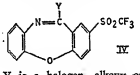
X signifies a hydroxyl group, a group of formula —OMe, wherein Me signifies a metal, halogen or tosyl, or

b) reacting a compound of formula V,



V

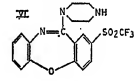
wherein A and R_1 are as defined above, with a compound of formula IV,



IV

wherein Y is a halogen, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms, sulphhydryl, p-nitrobenzylthio or tosyl, or

c) reacting the compound of formula VI



VI

with a compound of formula VII,

Z—A—O—CO—R_1 VII

wherein A and R_1 are as defined above, and Z is a halogen or tosyl.

2. A process for the production of a compound of formula I, stated in Claim 1, substantially as herein described with reference to any one of the Examples.

3. A compound of formula I, stated in Claim 1, whenever produced by a process according to Claim 1 or 2.

4. A compound of formula I, stated in Claim 1.

5. 2 - Trifluoromethylsulphonyl - 11 - (4-heptanoyloxyethyl - 1 - piperazinyl)dibenz-[b,f] [(1,4]oxazepine.

6. 2 - Trifluoromethylsulphonyl - 11 - (4-β - tetradecanoyloxyethyl - 1 - piperazinyl)-dibenz[b,f] [1,4]oxazepine.

7. 2 - Trifluoromethylsulphonyl - 11 - (4-β - butanoyloxyethyl - 1 - piperazinyl)dibenz-[b,f] [(1,4]oxazepine.

8. 2 - Trifluoromethylsulphonyl - 11 - (4-β - decanoyloxyethyl - 1 - piperazinyl)dibenz-[b,f] [(1,4]oxazepine.

9. A compound according to any one of Claims 3 to 8, in acid addition salt form.

10. A pharmaceutical composition comprising a compound of any one of claims 3 to 8 in free base form or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutically acceptable diluent or carrier.

11. A pharmaceutical composition according to Claim 10, substantially as herein described.

B. A. YORKE & CO.,
Chartered Patent Agents,
98 The Centre, Feltham,
Middlesex, TW13 4EP,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1974.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.